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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20

Application Number: 09/854,844
Filing Date: May 14, 2001
Appellant(s): HU ET AL.

David W. Hibler
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on July 3, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

Appellant's brief includes a statement that there are no related appeals or interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is substantially correct. However, it includes a statement in regard to the alleged uses of the present invention which is appropriately found in the argument's section of the Brief and will be addressed in the Response to Arguments section of this Answer.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. In regard to the rejection of claim 2 under 35 USC 112, second paragraph, upon further consideration, this rejection is hereby withdrawn.

(7) Grouping of Claims

The brief contains a statement indicating that claims in each of the issues shall stand or fall together as a group

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Bork, Genome Research, 10:398-400, 2000.

Broun et al., Science 282:1315-1317, 1998.

Brenner, TIG 15:132-1333, 1999.

Caughey, Am. R. Respir. Crit. Care Med. 150:5138-5142, 1994.

NCBI Annotation Project, GenBank accession number XM_093852, May 2002.

Plowman et al., GenBank accession number AX360076, February 2002.

Plowman et al., WO 02/00860, January 3, 2002.

Seffernick et al., J. Bacteriol. 183(8):2405-2410, 2001.

Smith et al., Nature Biotechnology 15:1222-1223, 1997.

Van de Loo et al., Proc. Natl. Acad. Sci. 92:6743-6747, 1995.

Walker et al., Cellular and Molecular Life Sciences 58:596-624, 2001.

Witkowski et al., Biochemistry 38:11643-11650, 1999.

Yamada et al., GenEMBL accession number AB018694, October 5, 1999.

Yamada et al., SPTREMBL accession number Q9PVX7, May 1, 2000.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-8 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 1-8 are directed to the polynucleotide of SEQ ID NO: 1, a polynucleotide encoding the polypeptide of SEQ ID NO: 2, a genus of polynucleotides comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1, expression vectors comprising said polynucleotides, and host cells comprising said expression vectors.

The specification discloses that the polynucleotide of SEQ ID NO: 1 encodes a protein (SEQ ID NO: 2) which shares structural similarities with mammalian proteases (page 1, lines 11-12), in particular serine proteases (page 2, lines 1-2). Based on structural similarity, Appellants assert that the claimed polynucleotides encode a new mammalian serine protease.

While the specification asserts that the polynucleotide of SEQ ID NO: 1 encodes a new protease, the claimed invention does not meet the utility requirements for the following reasons.

There is no experimental evidence to support the assertion that the claimed polynucleotides encode a polypeptide having serine protease activity. The alleged function for the claimed polynucleotides has been determined solely on the basis of structural similarity (i.e. sequence homology). The state of the art clearly teaches the unpredictability of assigning function based on sequence homology and acknowledges that small changes can drastically change function. Bork (Genome Research, 10:398-400, 2000), Smith et al. (Nature Biotechnology 15:1222-1223, 1997) and Brenner (TIG 15:132-1333, 1999) are some of the references which describe the overall state of the art in regard to the unpredictability of annotating function.

Bork teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of known error margins for high-throughput computational methods. Bork also indicates that one of the causes of this inaccuracy is that the quality of data available is still insufficient, especially data relating to protein function. Furthermore, Bork teaches that protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Smith et al. indicates that there are numerous cases in which proteins of very different functions are homologous (page 1222,

third column, last paragraph). In addition, Brenner teaches the difficulty of accurately inferring function from homology and clearly states that most homologs must have different molecular and cellular functions (column 2, second paragraph, page 132). Examples of pitfalls associated with comparative sequence analysis for predicting function are shown by Broun et al. (Science 282:1315-1317, 1998), Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995), Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) and Witkowski et al. (Biochemistry 38:11643-11650, 1999). Van de Loo et al. teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Broun et al. teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Witkowski et al. teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different biological function.

The polypeptide of SEQ ID NO: 2 shares at best 31.4% sequence homology with an epidermis specific serine protease from Xenopus laevis (African clawed frog) disclosed by Yamada et al. (SPTREMBL accession number Q9PVX7, May 2000) and the polynucleotide of SEQ ID NO: 1 shares at best 14.5% overall sequence homology with the polynucleotide encoding the polypeptide of Yamada et al. (GenEMBL accession number AB018694, October 1999). See attached alignments. In addition, the specification is silent in regard to the critical structural elements in the polynucleotide of SEQ ID NO: 1 or the polypeptide of SEQ ID NO: 2 which are indicative of serine protease activity. In view of the unpredictability of annotating function based on sequence homology, as evidenced by the teachings of Bork, Brenner, Smith et al., Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. as well as the low % sequence homology between the polynucleotides/polypeptide of the instant application and

polynucleotides/polypeptides of the prior art having serine protease function, one of skill in the art cannot reasonably conclude that the asserted function for the polypeptide encoded by the claimed polynucleotides is that of a serine protease absent additional supporting evidence such as an indication of which are the critical structural elements present in the claimed polynucleotides which are characteristic of other polynucleotides encoding serine proteases or even experimental evidence of the claimed function. In the instant case, the specification fails to provide any information or experimental evidence which would support Appellant's asserted biological function, other than the disclosure of the function of the closest structural homologs.

In addition, even if one assumes that the asserted function for the polypeptide encoded by the claimed polynucleotides is that of a serine protease, the specification fails to disclose sufficient information to conclude that there is a substantial and specific utility associated with the serine protease polynucleotide/polypeptide of the instant invention.

The specification discloses that proteases have been associated with development regulation, modulation of cellular processes, fertility and infectious diseases (page 1, lines 25-27). The specification also asserts that the claimed polynucleotides can be used for (1) screening and diagnosis (page 10, lines 20-33), (2) identification of coding sequences and mapping a unique gene to a particular chromosome (page 2, lines 23-26), (3) assessing gene expression patterns using microarrays or high-throughput chips (page 5, lines 18-21). While the specification asserts several uses for the claimed polynucleotides, these utilities are not considered substantial and specific for the following reasons. The specification fails to disclose sufficient information in regard to the biological significance and further characterization of the claimed polynucleotides and the protein encoded thereby, such as (1) the substrates of the alleged serine protease, (2) the biological processes or pathways in which the substrates or the polypeptide of SEQ ID NO: 2 are involved, (3) specific conditions/diseases associated with the expression, or lack thereof, of the polynucleotide of SEQ ID NO: 1, such that a specific use for the claimed polynucleotides would be

apparent. If information in regard to the biological role of the claimed invention were to be presented, several utilities could be apparent for the claimed polynucleotides and the corresponding polypeptide, such as production of the cleavage products, detection of the substrates in samples by detection of the cleavage products, or isolation of modulators which can be used to regulate the processes in which the alleged protease is involved. However, these utilities require additional information which is not presented by the specification. As known in the art and admitted by Appellants in the specification, proteases are associated with many different biological processes. Furthermore, serine proteases belong to a large and diverse family of proteins with diverse roles in many physiological and pathological processes, therefore one would expect a serine protease to be rather specific in regard to its target substrates. Since, the substrates, the cellular function of the serine protease and its target substrates, and the biological processes associated with the target substrates/serine protease are all unknown, the utilities recited in the specification are not substantial since they will require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. See e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The instant situation is analogous to the lack of substantial utility examples provided by MPEP § 2107.01 in that basic research is required to study the properties of the claimed polynucleotides and the corresponding polypeptide as well as the mechanisms in which the claimed polynucleotides are involved. In addition, while one could argue that some of the recited uses are specific, such as being a probe to be used in microarrays or in mapping of nucleotides in a particular chromosome, it is noted that these uses are not specific due to the fact that all other human polynucleotides can be used as probes in microarrays or in mapping of nucleotides in the chromosome. Since the instant specification does not disclose an specific and substantial "real world" use for the polynucleotide of SEQ ID NO: 1 or a polynucleotide encoding the polypeptide of SEQ ID NO: 2, then the claimed invention as disclosed does not meet the requirements of 35 U.S.C. §101 as being useful.

Claims Rejections – 35 USC §112, first paragraph – Enablement/Utility

Claims 1-8 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections – 35 USC §112, first paragraph – Written Description

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 5, and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 5, and 8 are directed to a genus of polynucleotides of any function comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1, vectors comprising said genus of polynucleotides, and host cells comprising said vectors. A sufficient written description of a genus requires that the specification describe the attributes and features of a sufficient number of species within the genus so that the described species are representative of the attributes and features of all members of the genus. A complete description of any species should include description of both the structure and function of the species. While the specification provides the structure of the polynucleotide of SEQ ID NO: 1 and asserts a function for the polypeptide encoded by the polynucleotide of SEQ ID NO: 1, the specification is silent in regard to the functions of other polynucleotides comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1. Clearly, the claimed genus is highly diverse in both structural and functional features. The only shared structural feature is a region of 24 contiguous

nucleotides of the polynucleotide of SEQ ID NO: 1. The structural features of the remainder of the polynucleotide (which can be of any length in view of the term "comprising") are completely undefined. Furthermore, clearly the genus encompasses many species with widely diverse functions as well. The genus would encompass polynucleotides encoding a protein having serine protease activity, such as the polynucleotide of SEQ ID NO: 1, polynucleotides that would function as probes and primers for isolation of polynucleotides encoding serine proteases, such as fragments of the polynucleotide of SEQ ID NO: 1, and polynucleotides which would encode proteins of different functions. It is also noted that the specification is silent in regard to the critical structural elements required in a polynucleotide to encode a polypeptide with serine protease activity nor has it disclosed which 24 nucleotides of the polynucleotide of SEQ ID NO: 1 are essential in a polynucleotide to encode a polypeptide encoding the only function disclosed, i.e. serine protease.

While one could argue that the claimed genus of polynucleotides, vectors and host cells are adequately described since one could obtained polynucleotides of similar function by sequence comparison using the polynucleotide structures described in the specification and the prior art, the state of the art teaches that sequence comparison alone should not be used to determine function and that small structural changes can drastically change function. As discussed above, Bork teaches that protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Smith et al. indicates that there are numerous cases in which proteins of very different functions are homologous (page 1222, third column, last paragraph). In addition, Brenner teaches the difficulty of accurately inferring function from homology and clearly states that most homologs must have different molecular and cellular functions (column 2, second paragraph, page 132). In regard to examples showing how small structural changes affect function, Witkowski et al. teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. teaches that polypeptides of approximately 67% homology

to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art, as described above, clearly teaches that a genus of polynucleotides, as the one claimed, can potentially have many different functions which cannot be inferred by structural homology alone. The specification only discloses a single species of the genus which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the claimed genus. Thus, one skilled in the art cannot reasonably conclude that Appellant had possession of the claimed invention at the time the instant application was filed.

Claim Rejections – 35 USC §112, first paragraph – Enablement

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Even if specific and substantial utility or well established utility is found for the polynucleotide of SEQ ID NO: 1, the following rejection applies. Claims 1, 5, and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6)

the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims encompasses any polynucleotide of any function comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1, vectors comprising said polynucleotides and host cells comprising said vectors. While the structure of the polynucleotide of SEQ ID NO: 1 is disclosed and a function has been asserted for the polypeptide encoded by the polynucleotide of SEQ ID NO: 1, the specification fails to disclose (1) other functions for all polynucleotides comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1, (2) critical structural elements required in a polynucleotide comprising at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1 to encode a protein with the only function disclosed in the specification, i.e. serine protease activity, (3) which 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1 are required in a polynucleotide to encode a polypeptide having serine protease activity, (4) or examples of other polynucleotides as encompassed by the claims with the exception of the polynucleotide of SEQ ID NO: 1.

The argument can be made that the claimed invention, i.e. polynucleotides of any function comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1, vectors and host cells, is enabled by the teachings of the specification and what is known in the prior art since one could obtained polynucleotides of similar function by sequence comparison using the structures disclosed in the specification and those of the prior art. However, as previously discussed, the state of the art teaches the unpredictability of properly assigning function based on structural homology. As discussed above, Bork teaches that protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Smith et al. indicates that there are numerous cases in which proteins of very different functions are homologous (page 1222, third column, last paragraph). In addition, Brenner teaches the difficulty of accurately inferring function from homology and clearly states that most homologs must have different molecular and cellular functions (column 2, second paragraph, page 132).

Furthermore, the art clearly teaches examples in support of the teachings of Bork, Brenner and Smith et al., which show how small structural changes result in changes in function, therefore indicating that structural homologs may not share a similar function. Witkowski et al. teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art, as described above, clearly teaches that even one amino acid substitution can result in a polypeptide having different function, therefore the claimed polynucleotides can potentially encode proteins of many different functions which cannot be inferred by structural homology alone.

Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to encode a protein of serine protease activity or which 24 contiguous nucleotides are required to encode a serine protease, and the unpredictability of the art in regard to assigning function based on structural homology, one of skill in the art would have to go through the burden of undue experimentation in order to (1) screen and isolate the extremely large number of polynucleotides encompassed by the claims to determine which encode proteins with serine protease activity, (2) determine the function of a potentially extremely large number of polynucleotides for which no function has been disclosed, and (3) determine how to use those polynucleotides of unknown function. Thus, Appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and/or use the invention as claimed.

(11) Response to Argument

A. Do Claims 1-8 lack patentable utility?

At the beginning of page 5 of the Brief, Appellants indicate that in response to the Final Action, Appellants pointed out that the present nucleic acids have utility in forensic analysis and that the specification (page 15, line 29-page 16, line 2) discloses two nucleotide polymorphisms at positions 343 and 868 of SEQ ID NO: 1. In view of the disclosure of these polymorphisms, Appellants conclude that the claimed polynucleotides must have a real world utility. In response to the Advisory Action, Appellants argue that the presently described polymorphisms can be used by those of skill in the art to distinguish between one person from another simply based on the presence or absence of such polymorphisms. It is Appellant's opinion that the Examiner has not provided any evidence to show that the claimed polynucleotides cannot be used in forensic analysis without any additional research. Appellants submit that since screening for these polymorphisms will provide additional information on the percentage of particular subpopulations that contain these polymorphic markers, this does not mean that additional research is needed for these markers to be used in forensic science. Therefore, Appellants conclude that the Examiner has failed to prove that the present invention lacks utility.

The Examiner acknowledges the disclosure of two polymorphisms in the specification. However, the Examiner disagrees with Appellant's contention that the claimed polynucleotides have utility in forensic analysis in view of the fact that neither the specification nor the art teaches how one can correlate the presence or absence of such polymorphisms with a specific identifying characteristic such as ethnic background, a specific disorder or a condition. As indicated in the Advisory Action and reiterated herein, one cannot reasonably conclude that the claimed polynucleotides can be used in forensic analysis if there is no teaching or suggestions as to how to distinguish one person from another. The presence or absence of such polymorphisms, in the absence of a correlation between the polymorphisms and some identifying characteristic, provides no real world use in forensic analysis. Furthermore, determining the correlation

between these polymorphisms and a specific identifying characteristic would require additional research since the specification provides no clue as to possible characteristics associated with the presence or absence of such polymorphisms. Thus, contrary to Appellant's assertion, the claimed polynucleotides lack utility as tools in forensic science.

In page 5 of the Brief, last paragraph, Appellants indicate that in response to the Final Action, Appellants pointed out that even in the worst case scenario, the polymorphisms described can be used to distinguish 50% of the population. In response to the Advisory Action, Appellants point out that distinguishing at least 50% of the population is an inherent feature of any polymorphic marker and that this feature is well understood by those of skill in the art. Appellants cite In re Wands to support the argument that a patent need not disclose what is well known in the art. Appellants also argue that because the Examiner has previously indicated that information in the art in regard to how one can use the disclosed polymorphisms as markers to distinguish 50% of the population has not been found, the Examiner seems to be suggesting that because their polynucleotides are novel, they lack utility. Furthermore, Appellants point out that forensic biologists use polymorphic markers such as those described by Appellants every day, therefore this fact is sufficient evidence to show that the polynucleotides of the instant invention can be used in the same fashion.

The Examiner acknowledges that a patent need not disclosed what is well known in the art and that any polynucleotide comprising a polymorphic marker can be used to distinguish a certain segment of the population. However, the Examiner disagrees with Appellant's contention that (1) the claimed polynucleotides have patentable utility, and (2) the Examiner has deemed the claimed invention to lack patentable utility because these polymorphisms are novel. While in principle any polymorphism can be used to distinguish one population from another, it is noted that neither the specification nor the art teaches which segment of the population can be distinguished by the disclosed polymorphisms or which are the characteristics common to those individuals carrying such polymorphisms. There is no disclosure

of the biological role of these polymorphisms either. While Appellants argue that the claimed polynucleotides can be used as markers to distinguish at least 50% of the population, there is no disclosure of which percentage of the population carries the disclosed polymorphism. Appellant's argument that the claimed polynucleotides have specific and substantial utility as markers in forensics since forensic biologists use polymorphic markers every day is not deemed persuasive in view of the fact that forensic biologists are able to use such polymorphic markers by associating their presence or absence with a specific identifying characteristic. In view of the fact that the specification has not disclosed any specific identifying characteristic associated with such polymorphisms, or even which percentage of the population carries these polymorphisms, and determining the correlation between these polymorphisms and an identifying characteristic would require additional research, one cannot reasonably conclude that the asserted utility in forensics is specific or substantial.

In page 6 of the Brief, last paragraph, Appellants submit that the Examiner is confusing the requirements of a specific utility with a unique utility. According to Appellants, the fact that other polymorphic markers have been identified in other loci or that the use of the instant polymorphisms will provide additional information concerning the prevalence of these markers in certain subpopulations does not mean that Appellant's identification of polymorphic markers in SEQ ID NO: 1 is not specific. Appellants cite *Carl Zeiss Stiftung v. Renishaw PLC* in support of the argument that because other polymorphic markers from the human genome have been described, the present polynucleotides lack specific utility. According to Appellants, the requirements for specific utility should not be confused with the requirement for a unique utility, which is not a legal standard. It is Appellant's opinion that if every invention were required to have a unique utility, the PTO would no longer issue patents on batteries, tires, etc and the class/subclass system would be an effort in futility. It is Appellant's opinion that in view of the arguments presented, there is no doubt that the claimed polynucleotides meet the requirements of 35 USC § 101.

The Examiner acknowledges the findings in *Carl Zeiss Stiftung v. Renishaw PLC* and agrees that the legal standard under 35 USC § 101 is specific and not unique. However, the Examiner disagrees with Appellant's contention that the Examiner has confused specific utility with unique utility. The Examiner is not contending that the claimed polynucleotides lack utility because other polymorphic markers have been described previously but rather due to the complete lack of information as to what is specifically being detected with these polymorphic markers, i.e. which populations are being distinguished by the presence or absence of these markers or which are the specific characteristics an individual carrying these markers should have. In the absence of this information, the asserted use of the claimed polynucleotides as polymorphic markers is not specific and substantial since all other polynucleotides also can be used as polymorphic markers. It is noted that what makes a polymorphic marker specific is its ability to distinguish a certain population from another or to identify an individual having a specific characteristic. This is analogous to a baseball bat, a hockey stick or a golf club being used as sticks but each having a specific use to play baseball, hockey or golf. Thus, the Examiner has not used the requirements for unique utility, as asserted by Appellants, in view of the fact that there is not even a description of the populations which can be distinguished by these polymorphic markers nor there is any information as to which identifying characteristics are associated with the presence or absence of these polymorphisms in an individual. The asserted utility as polymorphic markers is not a substantial utility in view of the fact that additional research is needed to identify which populations are associated with these polymorphic markers, and/or which characteristics are associated with the presence or absence of these polymorphisms, such as diseases, disorders, or ethnic background.

In page 7 of the Brief, last paragraph, Appellants cite *In re Brana* in support of the argument that while further research and development may be needed, this does not preclude a finding that the invention has utility. Appellants argue that the claimed polynucleotides are useful in forensic analysis without the need for any further research. Furthermore, Appellants submit that even if one uses the claimed

polynucleotides to determine which subpopulations contain these polymorphic markers, this does not constitute additional research since they have been already disclosed as having use in forensics. In addition, Appellants argue that even if further research is required in certain aspects of the invention, this does not render the claimed invention as lacking utility according to In re Brana. Appellants further cite *In re Angstadt and Griffin, Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* and *In re Wands* in support of the argument that a considerable amount of experimentation is permissible if such experimentation is routinely practiced in the art.

The Examiner acknowledges the findings in *In re Brana, In re Angstadt and Griffin, Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* and *In re Wands.* However, the Examiner disagrees with Appellant's contention that the claimed invention has utility in view of these findings. While it is agreed that FDA approval is not a requirement for finding a compound patentably useful and that routine experimentation does not render an invention unpatentable, it is noted that in the instant case, the utility rejection was not applied to the claimed invention because it failed to comply with government requirements to market the invention for human consumption or because some routine experimentation is required to practice the claimed invention. Instead, the utility rejection was applied due to the lack of information as to its biological function/use as discussed in claim rejections under 35 USC § 101 above. Furthermore, in regard to *In re Angstadt and Griffin,* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* even if one considers Appellant's assertion that the claimed polynucleotides can be used as polymorphic markers, in view of the complete lack of information as to which specific populations can be distinguished by the polymorphic markers disclosed, the biological role of these polymorphisms, or which identifying characteristics are associated with the absence or presence of these polymorphisms such that one can distinguish one individual from another, one of skill in the art cannot reasonably conclude that the additional research required to practice the claimed invention is merely routine experimentation. In regard to *In re Brana*, it is noted that "the expectation of further research and development" as recited in

the decision by the Federal Circuit refers to additional research to determine if the invention is safe and effective in humans, which are FDA requirements for market approval, and does not refer to further research and development to determine how to use the invention, which is the case herein. In regard to *In re Wands*, while it is agreed that one need not to disclose what is well known in the art, it is noted that neither the specification nor the state of the art describe or provide any information as to (1) the actual biological function of the polypeptide encoded by the claimed polynucleotides other than to indicate that the polypeptide of the instant invention is a serine protease, (2) the biological role of the polymorphisms disclosed, (3) which populations can be distinguished by the polymorphic markers disclosed, or (4) which identifying characteristics are associated with the presence or absence of these polymorphic markers. Since information which would enable one of skill in the art to practice the claimed invention is not known in the art, it is the specification which must provide the necessary information to enable the skilled artisan to practice the claimed invention.

In page 9 of the Brief, first paragraph, Appellants argue that while only one credible assertion of utility is needed to meet the requirements of 35 USC § 101, Appellants have indicated in responses to previous Office Actions, that the claimed polynucleotides have a specific utility in "identification of protein coding sequence" and "mapping a unique gene to a particular chromosome". According to Appellants, the polynucleotide of SEQ ID NO:1 can be used to map the 5 coding exons of the gene comprising the presently claimed polynucleotide on chromosome 4 (Exhibit A alignment). Appellants submit that only a small percentage of the genome contains exons and that the claimed polynucleotides provide biologically validated empirical data that specifically define that portion of the corresponding genomic locus encoding an exon. In addition, Appellants argue that the claimed polynucleotides define how the exons are actually spliced together to produce an active transcript. Appellants submit that these "biologically validated" splice junctions are superior to splice junctions that may have been predicted from genomic sequence alone, and that the specification teaches that sequences derived from regions

adjacent to intron/exon boundaries can be used in diagnostics and pharmacogenomics. Therefore, it is Appellant's conclusion that the practical scientific value of biologically validated mRNA sequences is readily apparent to those of skill in the art.

First, it is important to note that the specification does not provide any information as to the actual genomic locus (i.e. chromosomal position of the gene) which corresponds to the claimed polynucleotides. Exhibit A is an alignment of the polynucleotide of SEQ ID NO:1 and the sequence of chromosome 4 which was disclosed by a different party after the instant application was filed. While it is agreed that (1) the claimed polynucleotides can be used to detect the particular locus (i.e. position in the chromosome at which the gene resides) of the human genome where the gene encoding the polypeptide of SEQ ID NO: 2 is located, (2) a small portion of the genome contains exons, and (3) biologically validated splice junctions are superior to splice junctions that may have been predicted from genomic data alone, the Examiner disagrees with Appellant's contention that the asserted utilities, i.e. "identification of protein coding sequence" and "mapping a unique gene to a particular chromosome", are specific to the claimed polynucleotides. Even if one assumes that the instant polynucleotides can be used to detect exons in chromosome 4, it is noted that any human polynucleotide which encodes a protein can be used to detect the particular locus of the corresponding gene, therefore any human polynucleotide which encodes a protein can be used to detect exons as well as to determine the specific chromosome which contains that locus. In addition, while one could argue that the claimed polynucleotides can be used as markers to isolate the particular chromosome which contains the locus of the gene encoding the polypeptide of SEQ ID NO: 2 (encoded by the polynucleotide of SEQ ID NO:1), since that chromosome will contain many other genes, any polynucleotide which is complementary to any of those other genes will also serve as a marker for that particular chromosome. Similarly, any polynucleotide encoding a protein can be used to identify a protein coding sequence. Therefore, one cannot conclude that the asserted utilities are specific to the claimed polynucleotides. This situation is analogous to the examples provided in MPEP § 2107.01

in regard to what constitute a non-specific utility since, as stated MPEP § 2107.01 "a specific utility is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to a broad class of inventions". It is also noted that there is no disclosure in the specification as to any diseases, conditions or biological changes associated with modifications in the structure (i.e. mutations) of the gene encoding the polypeptide of SEQ ID NO: 2, which would lead one of skill in the art to use the claimed polynucleotides as probes to detect mutations in that specific locus (i.e. specific markers). While using the claimed polynucleotides to detect the corresponding gene in chromosome 4 (gene mapping) would be considered a specific utility if the biological function and/or specific condition associated with that particular locus of human chromosome 4 is known, or if some information is provided in regard to how the claimed polynucleotides are specific markers of the human genome, in the absence of such information, it is unclear as to how one of skill in the art can reasonably conclude that the asserted uses of the claimed polynucleotides are specific and substantial.

At the beginning of page 10 and continuing on page 11 of the Brief, Appellants argue that the claimed polynucleotides provide exquisite specificity in detecting specific regions of chromosome 4, which is a utility not shared by other polynucleotides. Appellants submit that early gene mapping techniques produced genetic maps with low resolution such that they would not be useful in identifying specific genes involved in disease. Therefore, it is Appellant's opinion that the claimed polynucleotides provide significant benefit as markers that map a specific locus of the human genome. Furthermore, Appellants submit Exhibit B (Venter et al., Science 291:1304-1351, 2001) to support the argument that the claimed polynucleotides provide information which is of great importance in structural analysis of genomic data. Appellants also argue that it is unclear to them as to what corroboration is required to confirm that the polynucleotide of SEQ ID NO:1 contains 5 exons. Appellants submit that they have conducted the same analysis used by those of skill in the art to determine the number of exons present in a cDNA, by comparing SEQ ID NO:1 to the sequence of human chromosome 4, as shown in Exhibit A.

Appellants conclude that in view of Exhibit A, there can be no doubt that the claimed polynucleotides can be used to map exons.

The Examiner acknowledges that (1) earlier mapping techniques may not provide high resolution, (2) the claimed polynucleotides can be used to detect human chromosome 4 and a particular locus in human chromosome 4, (3) information regarding expressed polynucleotides is of great importance in structural analysis of genomic data, and (4) the alignment of Exhibit A and SEQ ID NO:1 appears to indicate that the polynucleotide of SEQ ID NO:1 is contained in human chromosome 4. However, the Examiner disagrees with Appellant's contention that the claimed polynucleotides have utility for the following reasons. As indicated above and reiterated herein, while the polynucleotide of SEQ ID NO:1 can be used as a marker to detect human chromosome 4 since such chromosome contains the locus of the gene encoding the polypeptide of SEQ ID NO:2 (encoded by the polynucleotide of SEQ ID NO:1), chromosome 4 also contains other genes. As such, any polynucleotide which is complementary to any of those genes can be used as a marker of chromosome 4. Similarly, any of those genes contained in chromosome 4 can be used for gene mapping and would also have the ability to localize a particular region of such chromosome. Therefore, unless there is some information as to the biological role and/or the conditions/disorders associated with that particular locus in chromosome 4, or some information is provided in regard to how the claimed polynucleotides are specific markers of the human genome, the asserted uses of the claimed polynucleotides cannot be considered specific and substantial.

In regard to the importance of information in regard to coding sequences (i.e. which polynucleotides encode proteins), it is noted that it is the patentable utility of the specific polynucleotides claimed in the instant application and not the significance of additional information in regard to other coding sequences which is being determined and discussed. The Examiner is not disputing the importance of finding new protein-encoding polynucleotides for structural analysis of genomic data, but rather the patentable utility of specific polynucleotides encoding an alleged protease. While it is agreed

that the disclosure of an additional human polynucleotide provides more information in regard to the human genome, as indicated previously, in the absence of any additional information in regard to its biological function, the isolation of the human polynucleotides of the instant application is only useful as a starting point for researchers to further investigate its biological significance, therefore the utility of the instant polynucleotides, as clearly stated in MPEP § 2107.01 is not a "real world" substantial utility.

In regard to Appellant's opinion that the claimed polynucleotides provide biologically validated data in view of Exhibit A, it is noted that while it is agreed that the polynucleotide of SEQ ID NO:1 appears to be contained in chromosome 4, there is no corroboration that the polynucleotide of SEQ ID NO: 1 is indeed the actual transcript of a gene. According to the specification, the polynucleotide of SEQ ID NO: 1 was identified from a cDNA library using probes and/or primers generated from human gene trapped sequence tags (page 15, lines 20-25). As known in the art, cDNA libraries can contain cDNAs which may not be representative of the actual transcript of a gene (i.e. mRNA) since the PCR primers used in the construction of such libraries may contain parts of an intron and many other artifactual constructs can be produced during amplification of a library. As such, the cDNAs produced, while containing exons, may not be representative of an actual transcript as they may also contain parts of an intron or present artifactual junctions which are not naturally produced, therefore resulting in a wrong transcript of a gene. In the absence of additional experimental evidence corroborating that the claimed polynucleotides are indeed actual transcripts of a gene, one cannot reasonably conclude that the claimed polynucleotides provide biologically validated data.

In page 11 of the Brief, first paragraph, Appellants argue that while non-coding nucleotide sequences from this precise region of chromosome 4 could be used to map the introns and exons as described above, it would only be possible using the information provided by Appellants. Specifically, Appellants submit that one need to know which sequences correspond to the coding region in order to use non-coding sequences to map intron/exon junctions. It is Apppelant's opinion that using the information

provided by Appellants against them to question utility is a classic case of hindsight reconstruction. Furthermore, Appellants argue that the Examiner seems to be confusing the requirements of a specific utility with a unique utility and that while a small number of other polynucleotides can be used to map the protein coding regions in a particular region of chromosome 4, this does not mean that the use of Appellant's polynucleotides to map the protein coding regions of chromosome 4 is not specific.

As indicated above and reiterated herein, the Examiner is not contending that the claimed polynucleotides cannot be used to map human chromosome 4 or that the information provided by Appellants does not add to the knowledge of which protein-encoding polynucleotides are contained in human chromosome 4. However, the Examiner disagrees with Appellant's contention that (1) hindsight reconstruction has been applied to question the utility of the claimed invention, (2) knowing an additional protein-encoding polynucleotide or having a new polynucleotide which can be used to probe chromosome 4 is sufficient to meet the utility requirements under 35 USC § 101, or (3) the Examiner is confusing the requirements of a specific utility with a unique utility. It is unclear to the Examiner as to how hindsight reconstruction has been applied in determining lack of utility for the claimed invention if the Examiner has never indicated that the claimed polynucleotides cannot be used to map the human chromosome comprising said polynucleotides. It is reiterated herein that the claimed polynucleotides have been deemed as lacking patentable utility in view of the lack of information as to (1) their biological function, (2) diseases and/or conditions associated with their expression or lack thereof, or (3) how/which structural changes (i.e. polymorphisms) in such polynucleotides are markers for a specific condition or markers to distinguish a certain population. Appellant's asserted use for the claimed polynucleotides as probes to map a particular locus within chromosome 4 is not a patentable utility, since as indicated above, in the absence of a biological function and/or the conditions/disorders associated with that particular locus in chromosome 4, or some information is provided in regard to how the claimed polynucleotides are specific markers of the human genome, such use is not specific or substantial.

In regard to Appellant's opinion that the Examiner has confused the requirements of a specific utility with a unique utility, it is reiterated that the Examiner has not used the requirements for unique utility, as asserted by Appellants, in view of the fact that other genes contained in chromosome 4 can be used as markers of chromosome 4. Furthermore, the specification is completely silent in regard to the biological significance of the specific locus to which the polynucleotide of SEQ ID NO: 1 belongs to. Since determining the biological role and/or conditions associated with that particular locus would require further research, the asserted use is not deemed as a substantial utility.

In page 11 of the Brief, last paragraph, Appellants argue that additional polynucleotides/polypeptides having sequences sharing 99% homology to that of SEQ ID NO: 1 or SEQ ID NO: 2 (sequence of the polypeptide encoded by the polynucleotide of SEQ ID NO: 1) have been annotated by third party scientists wholly unaffiliated with Appellants as polynucleotides encoding proteases. Appellants submit Exhibit C, showing an alignment of the polypeptide of SEQ ID NO: 2 and the polypeptide corresponding to GenBank's accession number XM_093852, and Exhibit D, showing an alignment of the polypeptide of SEQ ID NO: 2 and the polypeptide corresponding to GenBank's accession number AX360076. Appellants argue that the legal test for utility simply involves an assessment of whether those of skill in the art would find any of the utilities described to be credible or believable. Therefore, in view of these GenBank citations, it is Appellant's contention that there can be no doubt that those of skill in the art would believe that Appellant's polynucleotides encode a serine protease.

First, it is important to note that the specification does not disclose the polypeptides corresponding to GenBank's accession numbers XM_093852 (NCBI annotation Project) or AX360076 (Plowman et al.) as structural homologs of the polynucleotide of SEQ ID NO: 1 or the polypeptide of SEQ ID NO: 2. In fact, these GenBank's citations were not in GenBank's records at the time the first Office Action (Paper No. 7) was mailed on 12/3/2001 since they were first disclosed on May 2002

(XM_093852) and February 2002 (AX360076) as indicated in the corresponding entry records (GenBank). The citation corresponding to GenBank's accession number XM_093852 was first brought to the attention of the Examiner in response to the non-final rejection of Paper No. 7 and the actual sequence alignments were first submitted to the Examiner in response to the non-final rejection of Paper No. 10, mailed on 5/7/2002. In regard to the submission of an alignment of the polypeptide corresponding to GenBank's accession number AX360076 and the polypeptide of SEQ ID NO: 2, this is the first time GenBank's accession number AX360076 or the corresponding alignment has been brought to the attention of the Examiner.

While it is agreed that, according to the alignments presented by Appellants shown in Exhibit C and Exhibit D, the polypeptide of SEQ ID NO: 2 is highly homologous to the polypeptides encoded by the polynucleotides cited as GenBank's accession numbers XM_093852 or AX360076, the annotations of GenBank's XM_093852 and AX360076 in regard to the function of the polypeptides as a protease is also based solely on sequence homology. As indicated in the disclosure found under "Comment" in GenBank's entry XM_093852, it is stated that the function was predicted by automated computational analysis using gene prediction method Genome Scan. Similarly, the patent publication WO 0200860, which discloses GenBank's entry AX360076, teaches that the function of the polypeptide encoded by the polynucleotide of SEQ ID NO:32 (same as AX360076; see "Definition" in GenBank's entry) has been determined by sequence homology, as shown in page 179, lines 16-28 of the WIPO document. No experimental evidence has been shown in WO 0200860 which would indicate that the polypeptide encoded by the polynucleotide of GenBank's entry AX360076 is indeed a serine protease or its substrate. It is noted that only the relevant pages are being submitted with this document in view of the fact that the complete WIPO document is over 300 pages long. In view of this evidence, the functional annotations found in GenBank's XM_093852 and AX360076 are based on virtually the same information as are the assertions made by Appellants in the specification and add nothing to the record in support for

Appellant's position. Therefore, at best a skilled artisan would believe that the polypeptide encoded by the claimed polynucleotides could be placed in the broad general class of proteases but no specific function beyond that can be presumed. In view of the uncertainty in regard to the real function of the polypeptides encoded by the polynucleotides of GenBank's entries XM_093852 and AX360076, and in view of the unpredictability of the art in regard to assigning function based on sequence homology as evidenced by Bork, Brenner, Smith et al., Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. already discussed above, it is not reasonable for one of skill in the art to conclude that Appellant's polynucleotides have a specific and substantial or well-established utility.

In page 12 and continuing on page 13 of the Brief, Appellants argue that the Examiner has repeatedly questioned Appellant's assertion that the claimed polynucleotides encode a serine protease. Appellants refer to Bork (Genome Research, 10:398-400, 2000) and indicate that even if one assumes that greater than 70% sequence homology is required for one of skill in the art to believe that a polynucleotide encodes a polypeptide of a certain activity, the claimed polynucleotides have exceeded the Examiner's arbitrary threshold of sequence relatedness. Appellants also point out that the Bork article relates to the 70% accuracy of the resulting prediction and not 70% homology. According to Appellants, Smith et al. (Nature Biotechnology 15:1222-1223, 1997) et al., teaches that the major problems associated with nearly all of the current automated annotation approaches are minor annotation inconsistencies and a few errors. Therefore, it is Appellant's position that Smith et al. does not seem to stand for the proposition that prediction of function based on homology is fraught with uncertainty. In regard to Brenner (TIG 15:132-1333, 1999), Appellants submit that Brenner's statement in regard to most homologs having different molecular and cellular functions is based on the assumption that only 1000 superfamilies exist in nature and that Brenner teaches that one of the main problems associated with using homology to predict function is an issue solvable by appropriate use of modern and accurate sequence comparison procedures such as those used by Appellants. Appellants argue that the teachings of Broun et al. (Science 282:1315-

1317, 1998) and Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) only refer to one example where function based on sequence homology proved to be incorrect and that one example out of thousands of predictions of function based on structural homology is hardly indicative of a high level of uncertainty. It is Appellant's contention that while the Examiner has cited articles by Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) and Witkowski et al. (Biochemistry 38:11643-11650, 1999) to support the proposition that prediction of protein function based on homology is unpredictable, the Examiner has not provided evidence that directly establishes that the specifically claimed polynucleotides do not encode a serine protease. It is Appellant's opinion that they have provided evidence of record that conclusively establishes that those of skill in the art would believe that the claimed polynucleotides encode a serine protease.

The Examiner disagrees with Appellant's contention that since the claimed polynucleotides have exceeded a 70% sequence relatedness threshold to polynucleotides which have been annotated as encoding proteases, one of skill in the art would reasonably conclude that the claimed polynucleotides also encode proteins of specific biological function. As indicated above, the annotated function for the polypeptides encoded by the polynucleotides of GenBank's entries XM_093852 and AX360076 has been determined solely on sequence homology and no experimental corroboration has been provided in regard to their biological function. The closest homolog of the polypeptide of SEQ ID NO: 2 having experimentally determined serine protease activity is that of Yamada et al. (GenEMBL accession number AB018694, October 1999), which is at best 31.4% sequence homologous to the polypeptide of SEQ ID NO: 2. See discussion above. Therefore, while it is agreed that there is a high degree of structural homology between the polynucleotide of SEQ ID NO: 1 and those of GenBank's entries XM_093852 and AX360076, in the absence of any additional evidence corroborating its function or any information as to its substrate or its biological role, and considering the unpredictability of the art in regard to assigning function based on structural homology, one of skill in the art cannot reasonably conclude that there is a

specific biological function associated with the claimed polynucleotides. It is reiterated that at best, one of skill in the art would conclude that the polypeptide of SEQ ID NO: 2 may belong to a broad general class of proteases but no specific function beyond that can be presumed. In regard to the teachings of Bork, while it is agreed that the instant reference refers to 70% accuracy of prediction, this does not in any way oppose Bork's teachings in regard to the pitfalls associated with comparative sequence analysis for predicting protein function because of known error margins for high-throughput computational errors and the insufficient quality of data available in regard to protein function.

The Examiner acknowledges the teachings of Smith et al. in regard to the major problems associated with nearly all of the current automated annotation approaches, especially when dealing with large and complex protein families. However, the Examiner disagrees with Appellant's contention that the teachings of Smith et al. do not support the argument that, at this point in time, annotation of function based on structural homology is unpredictable. It is clear from the teachings pointed out by Appellants that there are problems with automated annotation of function, and while Smith et al. conclude that some of these problems are associated with inconsistencies in the databases and a few errors, nowhere in the cited reference there is a teaching or suggestion that these inconsistencies or errors have been fixed such that function annotation is now highly predictable, or that annotating function based on structural homology using the current annotation system would likely result in accurate estimation of function of any gene. While one of skill in the art is more likely to conclude that a structural homolog is potentially a functional homolog if there is high structural homology, when the structural homology is low, as is the case herein, one of skill in the art cannot not reasonably conclude that structural homologs are also functional homologs. At best, one can conclude that the structural homologs may belong to a broad general functional class.

In regard to the teachings of Brenner, while it is agreed that the instant reference teaches that if there are only about 1000 major superfamilies in nature, then most homologs must have different

molecular and cellular functions, it is unclear to the Examiner as to why this statement would not support the argument that there is unpredictability in assigning function based on sequence homology since it appears that there are about a total of 1000 superfamilies in nature, according to reference 11 (Chothia, 1992, Nature 357:543-544) and 12 (Brenner, 1997, Curr. Opin. Struct. Biol. 7:369-376), cited by Brenner in page 132, second column, line 32 . Therefore, Brenner teaches that taking into account all of the superfamilies known in nature, most homologs must have different molecular and cellular functions. The Examiner disagrees with Appellant's contention that the instant reference teaches that one of the main problems in using homology to predict function is an issue solvable by appropriate use of modern and accurate sequence comparison procedures. Instead, the instant references teaches the following: "It may be that the similarity between the genomic query and database sequence is insufficient to reliably detect homology, an issue solvable by appropriate use of modern and accurate sequence comparison procedures. A more difficult problem is accurate inference of function from homology" (page 132, column 2, lines 24-29). Therefore, contrary to Appellant's assertions, the teachings of Brenner clearly support the Examiner's position that there is unpredictability in accurate assignment of function based on sequence homology.

In regard to Appellant's comments in reference to the teachings of Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al., while it is agreed that the instant references do not specifically teach that the claimed polynucleotides do not encode a serine protease, it is noted that the Examiner clearly indicated that these references are specific examples of the art which provide support to the general consensus, as disclosed in Bork, Brenner and Smith et al., that accurate function annotation based on structural homology is still unpredictable. Therefore, contrary to Appellant's assertion that only one example is hardly indicative of a high level of uncertainty, the Examiner has provided four specific examples of enzymatic activity which was mistakenly predicted by structural homology as well as three references which discuss the general state of the art in regard to the accuracy of function annotation based

on structural homology (i.e. sequence homology). In addition, the Examiner disagrees with Appellant's contention that they have provided evidence of record that conclusively establishes that one of skill in the art would believe that the claimed polynucleotides encode a serine protease since (1) the annotated function for the polypeptides encoded by the polynucleotides of GenBank's entries XM_093852 and AX360076 is based solely on structural homology, as is the case with the claimed polynucleotides, (2) the closest homolog to the polypeptide of SEQ ID NO: 2 having experimentally determined serine protease activity is at best 31.4% sequence homologous to the polypeptide of SEQ ID NO: 2, (3) no additional information/evidence such as experimental determination of serine protease activity has been provided which further supports Appellant's assertion of serine protease function, and (4) the specification is completely silent in regard to its specificity, substrate or its biological role. Therefore, in view of the evidence provided and the teachings of the art in regard to the unpredictability of assigning function based on structural homology, one cannot reasonably conclude that the claimed polynucleotides have specific and substantial utility.

In page 13 of the Brief, last paragraph and continuing in page 14, Appellants argue that the PTO has repeatedly attempted to deny the utility of the claimed polynucleotides based on a small number of publications. Appellant submit that while they are not disputing that there is no100% consensus within the scientific community regarding prediction of protein function from homology information, this is completely irrelevant since the 100% accuracy of prediction of protein function based on structural homology is not the standard for patentability under 35 USC § 101. Instead, Appellants assert that the legal test for utility is whether those of skill in the art would find any of the utilities described for the invention to be believable. Appellants argue that the overwhelming majority of those of skill in the art would believe prediction of protein function from homology information and the usefulness of bioinformatic predictions. As such, one of skill in the art would believe that Appellant's polynucleotides encode a serine protease. It is Appellant's opinion that the claims meet the requirements of 35 USC § 101

since believability is the standard for meeting the requirements of 35 USC § 101 and not 100% consensus or 100% accuracy.

As indicated above, the Examiner has presented four specific examples of enzymatic activity which was mistakenly predicted by structural homology as well as three references which discuss the general state of the art in regard to the accuracy of function annotation based on structural homology (i.e. sequence homology). Therefore, it is deemed that a sufficient number of references have been provided to support the Examiner's position in regard to the unpredictability of assigning function based on structural homology. The Examiner is not contending that 100% accuracy of prediction is the standard for patentability under 35 USC § 101 or that one of skill in the art would not recognize the usefulness of bioinformatic predictions. Also, the Examiner is not contending that there are not instances where function has been accurately predicted based on structural homology nor stating that structural homology is never sufficient for one of skill in the art to believe an assertion of function based thereon. However, as taught by the art presented by the Examiner, at the present time, with the tools currently available, there is no general consensus as to which genes are going to be easier to annotate using structural homology or which are the conditions required for functional annotation using structural homology to be highly predictable for any gene, except for the level of structural homology. As shown by the examples provided by the Examiner, even structural homologies ranging from about 60% to 98% have been found to be not sufficient to accurately predict function in all instances. While the Examiner has presented examples where even 1 amino acid substitution can result in a different function, one of skill in the art is more likely to conclude that a particular polynucleotide encodes a protein of a certain function if the functional homologs have a high degree of structural (i.e. sequence) similarity or if certain motifs specific to that function are present. In the instant case, however, the closest experimentally determined functional homolog of the polypeptide of SEQ ID NO: 2 is at best 31.4% sequence homologous and the specification is silent in regard to which are the structural elements in the polypeptide of SEQ ID NO: 2

that are associated to serine protease activity. This very low level of homology is such that a skilled artisan would not find the assertion in regard to the function of the polypeptide of SEQ ID NO: 2 believable, absent some further corroborating evidence.

The requirements under 35 USC § 101 and the current utility guidelines are that the claimed invention should have a credible, specific and substantial, or a well established utility. While credibility is not been questioned herein, it is noted that for the reasons previously discussed above in regard to polymorphic markers, gene mapping and identification of protein encoding sequences as well as the lack of information in regard to the specificity of the alleged serine protease or its biological role, the claimed invention has not been found to have a specific utility. Also, in view of the extremely low sequence homology between the polypeptide of SEQ ID NO: 2 and the closest experimentally-determined serine protease homolog, the lack of supporting evidence in regard to the asserted biological function, the lack of information as to the specificity of the serine protease, its substrate or its biological role, and the unpredictability of the art in regard to accurately determining function based on structural homology, further research would be required to determine if indeed the claimed polynucleotides encode a serine protease, and if so, which are its substrates and its specificity. Therefore, the asserted utility is not considered a substantial utility. It is also noted that additional research would also be required to find a specific utility for the claimed polynucleotides since the specification is completely silent in regard to the specificity, substrates, and/or biological role of the alleged serine protease. Thus, contrary to Appellant's assertion, the claims do not meet the utility requirements under 3 5USC § 101.

In page 14 of the Brief and continuing in page 15, Appellants argue that one of skill in the art would recognize the importance of tracking the expression of the gene encoding the described protein in high-throughput DNA chips and that such DNA chips clearly have utility as evidenced by hundreds of issued patents, as exemplified by Exhibits E, F, G, H, I and J. Appellants argue that evidence of real world substantial utility is provided by the fact that there is an entire industry established based on the use

of gene sequences or fragments thereof in a gene chip format. Appellants further indicate that many companies have used gene chip technology and that one of such companies was recently purchased for significant amounts of money, therefore demonstrating that the real world industrial utility of gene sequences and fragments thereof is widespread and well-established. According to Appellants, given the widespread utility of gene chips which use public domain gene sequence information, there can be no doubt that the claimed polynucleotides would be of great utility in DNA chip applications. It is Appellant's opinion that since the claimed polynucleotides are specific markers of the human genome and targets for drug discovery, one of skill in the art would instantly recognize that the present nucleotide sequences would be ideal, novel candidates for assessing gene expression in gene chips. Appellants conclude that compositions that enhance the utility of such DNA chips, such as the claimed polynucleotides, must be useful. Thus, it is Appellant's position that the instant claims meet the requirements of 35 USC § 101.

While it is agreed that (1) there is an industry based on the use of polynucleotides and fragments thereof, (2) there are many billions of dollars invested in companies which use DNA chips and related technologies, (3) the use of polynucleotides in DNA chips (i.e. microarrays) is widespread, and (4) the claimed polynucleotides can be attached to DNA chips, it is noted that it is the patentable utility of the specific polynucleotides claimed in the instant application and not the general utility of DNA chips, polynucleotides or fragments, which is being determined and discussed. The Examiner is not disputing the patentable utility of DNA chips as a collection of polynucleotides linked to a solid support but rather the patentable utility of specific polynucleotides encoding an alleged serine protease. The Examiner acknowledges the hundreds of issued patents in regard to DNA chips however it is noted that the instant claims are not drawn to methods of use of DNA chips or to DNA chips (microarrays) but rather to specific polynucleotides. Furthermore, the asserted use of the claimed polynucleotides in DNA chips is

not specific since as Appellants have stated, many other polynucleotides including those in the public domain can and are used in DNA chips.

As indicated by the Examiner in previous Office Actions, for the claimed polynucleotides to be specifically useful in DNA chip applications, one would require some knowledge or guidance as to the biological role of the polypeptide encoded by such polynucleotides to effectively use the information gathered in tracking the expression patterns of such polynucleotides. The reduction or increase in expression of a polynucleotide is meaningless unless one can link changes in expression with some biological function. For example, if one were to use the claimed polynucleotides in assays which would lead to the discovery of drugs of a specific condition, such as an assay which uses a DNA chip to evaluate expression patterns upon exposure to a test compound, one need to know which diseases and/or biological functions are associated with the expression of such polynucleotides. Otherwise, one of skill in the art would have to carry out further experimentation to determine which are the conditions (i.e. diseases) and/or biological functions associated with the claimed polynucleotides. Appellant's contention that the claimed polynucleotides have utility in gene chip applications since they are specific markers which are targets for discovering drugs associated with human disease is not persuasive since the specification is silent in regard to (1) the conditions and/or biological functions which are associated with the expression of the claimed polynucleotides, (2) whether increase or decrease in expression correlates with disease, (3) which levels of increase or decrease in expression of the claimed polynucleotides are indicative of the presence or absence of a disease, and (4) how is the claimed invention a marker of the human genome. This is analogous to the examples provided by MPEP § 2107.01 in regard to what constitutes carrying out further research to identify or reasonably confirm a "real world" context of use since basic research is required to determine the properties or the mechanisms in which the claimed product is involved. Therefore, it is unclear how one of skill in the art can reasonably conclude that the asserted use of the claimed polynucleotides in DNA chips is a specific and substantial utility.

In page 15 of the Brief, Appellants argue that expression profiling does not require knowledge of function of the particular nucleic acid on the chip and that the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. According to Appellants, skilled artisans continue to use polynucleotides such as those of the instant invention in gene chips without undue experimentation. It is Appellant's opinion that while additional information concerning the claimed polynucleotides would make the invention more useful in certain gene chips, this does not mean that Appellant's asserted utility in gene chips is not specific.

While it is agreed that (1) skilled artisans would know how to operate a generic DNA chip, (2) one can monitor the expression levels of different polynucleotides in a DNA chip, and (3) a DNA chip indicates which DNAs are expressed at greater or lesser levels in different tissue types, the Examiner disagrees with Appellant's contention that the asserted utility for the claimed polynucleotides is specific. In addition, it is reiterated that it is not the patentability of DNA chips which is being examined and determined herein but rather the patentability of polynucleotides encoding an alleged serine protease. It has been previously indicated that the asserted utility for the claimed polynucleotides in DNA chips would be considered specific only if one could link the expression of the claimed polynucleotides, or lack thereof, with some biological function or condition since monitoring the reduction or increase in expression of a polynucleotide (i.e. expression profiling) is meaningless unless one can link changes in expression with some biological function. In the instant case, further research would be required to confirm a real world use in view of the fact that the amount of information provided is not sufficient to reasonably conclude that claimed polynucleotide encodes a serine protease. Even if one assumes that the claimed polynucleotides encode a serine protease, the specification is completely silent in regard to (1) specificity, (2) substrates, (3) biological function, or (4) conditions/disorders associated with the alleged serine protease. In view of the fact that essential information is missing, the asserted utility of the claimed polynucleotides in a DNA chip is not found to be specific and substantial.

At the last line of page 15 and continuing in page 16 of the Brief, Appellants argue that one of skill in the art as well as venture capitalists and investors can recognize the utility of genomic data in general, and specifically human genomic data. Appellants submit articles by Venter et al. and Jasny et al. in Exhibits B and K, respectively, to support their argument that the usefulness of human genomic data, including the claimed polynucleotides, is substantial and credible, since it is worth billions of dollars and has resulted in the creation of many companies, and well-established, since the utility of human genomic information has been clearly understood for many years. Appellants further cite *In re Lager* and *In re Marzocchi* in support of the argument that a statement of utility in a specification must be accepted unless there is reason to doubt the objective truth of the statement.

While the Examiner acknowledges that (1) one of skill in the art as well as venture capitalist and investors can recognize the utility of genomic data, (2) the teachings of Venter et al. and Jasny et al, (3) billions of dollars have been spent in the generation of human genomic data, (4) numerous companies worth billions of dollars have been created which are focused on human genome data, and (5) the utility of human genomic data has been understood for many years, Appellant's arguments have not been found persuasive for the following reasons. First, it is noted that commercial success is not one of the requirements for utility under 35 USC § 101. The Examiner is not disputing that one of skill in the art can see the potential usefulness of information coming out of the human genome project, however it is also known in the art that this information is valuable to the extent that it provides a starting point for scientists to further investigate the biological significance of the genetic information collected and possibly discover how to treat many conditions and diseases. In fact, while the potential usefulness of human genomic data was enormous, the lack of an immediate use for human genomic data was the primary reason why it was the federal government and not a private entity who first provided funding for the Human Genome Project. While it is agreed that the disclosure of an additional human polynucleotide provides more information in regard to the human genome, as indicated previously, in the absence of any

additional information in regard to its biological function, the isolation of the human polynucleotides of the instant application is only useful as a starting point for researchers to further investigate its biological significance, therefore the utility of the instant polynucleotides, as clearly stated in MPEP § 2107.01 is not a "real world" substantial utility. In regard to the findings in *In re Lager* and *In re Marzocchi*, it is reiterated that credibility has not been assessed. The Examiner deemed the claimed invention as lacking utility in view of the fact that the claimed polynucleotides do not have a specific and substantial or well-established utility, for the reasons discussed above.

In page 16 of the Brief, last paragraph, Appellants argue that the Federal Circuit in *Juicy Whip Inc. v. Orange Bang, Inc.* has stated that the threshold of utility is not high and that an invention is useful under section 101 if it is capable of providing some identifiable benefit. Appellants further cite *Brooktree Corp. v. Advanced Micro Devices, Inc.* to indicate that the Federal Circuit has stated that a claimed device must be totally incapable of achieving a useful result to lack utility under 35 USC § 101. Appellants cite *Cross v. Iizuka* in support of the argument that any utility for a claimed invention is sufficient to satisfy the requirements of 35 USC § 101 and indicate that the Federal Circuit has confirmed that anything under the sun made by man is patentable in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*

The Examiner acknowledges the numerous cases cited by Appellants wherein issues in regard to 35 USC § 101 were examined. It is noted however that only *Cross v. Iizuka* is considered relevant to the instant discussion since the inventions in that case are chemical compounds. In *Juicy Whip Inc. v. Orange Bang, Inc.*, the issue of utility was discussed in regard to a juice dispenser, *in Brooktree Corp. v. Advanced Micro Devices, Inc.*, the issue of utility was discussed in regard to a digital to analog conversion circuitry, and in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, the issue of utility was discussed in regard to a business method.

In *Cross v Iizuka*, the issues which the Federal Circuit had to examined were whether the Board erred in finding that the utility disclosed in the Japanese priority application by Iizuka is sufficient to meet

the practical utility requirement of 35 U.S.C. §101 and whether the Board erred in finding that the Japanese priority application contained sufficient disclosure to satisfy the enablement, i.e., how-to-use, requirement of 35 U.S.C. § 112. The PTO, the Board of Patent Appeals and Interferences and the Federal Circuit found that the claimed imidazole derivative compounds had practical *in vitro* utility since in addition to the disclosure of the structure of the claimed imidazole derivative compounds, there was experimental evidence of the strong inhibition of thromboxane synthetase by these imidazole derivatives in human and bovine microsomes. Thromboxane synthetase is an enzyme which leads to the formation of thromboxane A 2, which at the time the applications of Cross and Iizuka were filed, was postulated to be a causal factor in platelet aggregation, which in turn, is known to be associated with platelet thrombosis, pulmonary vasoconstriction or vasospasm, inflammation, hypertension, and collagen-induced thrombosis. In contrast, the instant application discloses the structure of the claimed polynucleotides and no biological characterization of the polypeptide encoded by the claimed polynucleotides other than to state that based on sequence homology it appears to be a serine protease. For the reasons indicated above, even if one assumes that the polypeptide encoded by the claimed polynucleotides is a serine protease, the specification fails to provide sufficient information for one of skill in the art to know how to use the claimed invention. The specification is silent in regard to (1) the specificity of the alleged serine protease and/or its substrates, (2) the biological processes or pathways in which the alleged serine protease is involved, or (3) the disorders or conditions associated with the alleged serine protease. Information in regard to biological function and/or condition/disorders associated with the alleged serine protease is essential for the asserted utility in DNA chips or gene mapping, to be specific and substantial for the reasons already discussed above. While one of skill in the art can reasonably conclude that the chemical compounds of Iizuka had a credible, specific and substantial utility, i.e. the imidazole derivative compounds inhibit an specific enzyme, thromboxane synthetase, in human and bovine microsomes, a

skilled artisan cannot reasonably conclude that the claimed polynucleotides have a specific and substantial utility or a well-established utility in view of the evidence presented.

In page 17 of the Brief, Appellants indicate that while they are aware of the new utility guidelines set forth by the USPTO, the current rules and regulations are the patent laws set forth in 35 USC and the rules set forth in 37 CFR but not the Manual of Patent Examination Procedure (MPEP) set forth by the USPTO. Furthermore, Appellants argue that it is the job of the judiciary and not the USPTO to interpret these laws and rules. Appellants argue that there are no recent changes in either 35 USC § 101 or in the interpretation of 35 USC § 101 by the Supreme Court or the Federal Circuit which support the new utility guidelines set forth by the USPTO and submit examples of US patents in Exhibit L, M, N and O, which, according to Appellants, do not comply with the new utility guidelines. While Appellants admit that each application is examined on its own merits, Appellants conclude that holding them to a different standard of utility is a clear violation of due process due to the similarity in subject matter between the claimed invention and the inventions in US patents of Exhibit L, M, N and O.

Appellants are reminded that the Examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the Examiner has no authority to disregard such guidelines or to apply her own interpretation of patent law in the examination of the application. Furthermore, as set forth in the guidelines and the MPEP, the guidelines were promulgated by the PTO in accordance with all applicable case law and thus are believed to be consistent therewith. While the Examiner acknowledges the US patents of Exhibits L, M, N and O, as indicated in previous Office Action Paper No. 13 (Final Rejection), mailed on 12/2/2002 and Paper No. 17 (Advisory Action), mailed on 4/29/2003, each application is examined on its own merits according to the current guidelines of examination as set forth by the USPTO and a discussion on the utility of any polynucleotide claimed in such patents would require a detailed review of the record of each individual case, which would be

improper herein. Finally, Appellants are further reminded that the Examiner has no authority to comment in regard to the legality of the new utility guidelines or the MPEP as set forth by the USPTO.

B. Are Claims 1-8 unusable due to a lack of patentable utility?

At the beginning of page 18 of the Brief, Appellants indicate that arguments detailed in section VIII(A) of the Brief are incorporated by reference due to the fact that it has been determined by the courts that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph have the same basis. Appellants argue that since claims 1-8 have been shown to have a "specific, substantial and credible utility" as indicated in section VIII(A), the present rejections under 35 USC 112, first paragraph cannot stand.

As indicated by Appellants, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

C. Is Claim 2 indefinite?

In page 18 of the Brief, last paragraph, and the beginning of page 19, Appellants indicate that a claim need not describe the invention, such description being the role of the disclosure. Appellants assert that one of skill in the art would understand how a nucleotide sequence could hybridize and that the term "the complement" refers to the complete complement of SEQ ID NO: 1. Therefore, Appellants assert that the claims are definite when read in light of the specification. Appellants submit that the USPTO has issued several patents as shown in Exhibit P, Q, R, S, T, U, V, W and X, which share the same assignee as that of the instant application, containing the same language as that found indefinite in the present case. Therefore, Appellants submit that claim 2 must also meet the requirements of 35 USC 112, second paragraph.

Appellant's arguments have been fully considered. While the term "sequence" as known in the art, refers to a graphical representation of the order in which nucleotides/amino acids are arranged in a molecule, the Examiner acknowledges the widespread use of this term as synonymous to "nucleic acid". In regard to the term "complement", the Examiner acknowledges Appellant's assertion that that the intended meaning of the term, within the context of claim 2, is "complete complement". As such, upon further consideration, this rejection is hereby withdrawn.

D. Do claims 1, 5 and 8 lack sufficient written description?

At the beginning of page 20 of the Brief, Appellants submit that the Examiner seems to require that the function of each of the members of the genus be known to satisfy the written description requirement. It is Appellant's opinion that the Examiner has completely misread the written description requirement and that the repeated citations of Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. are completely irrelevant to the question of compliance with 35 USC 112, first paragraph. Appellants submit that the written description requirements can be satisfied by (1) actual reduction to practice, (2) reduction to drawing, (3) disclosure of relevant, identifying characteristics, (4) structure or other physical and/or chemical properties, (5) by functional characteristics coupled with a known or disclosed correlation between function and structure, or (6) by a combination of such identifying characteristics. Thus, it is Appellant's opinion that the written description requirements can be satisfied by (1), (2) or (3), and part (3) can be satisfied by (4), (5) or (6). In the instant case, Appellants submit that claim 1 provides the nucleotide sequence itself as a "structure or other physical or chemical properties" and that there is no requirement within part (4) as described above, for functional characteristics, which are only required in (5) and (6) only. As such, it is Appellant's position that claims 1, 5 and 8 meet the written description requirement since they satisfy part (3) by satisfying part (4).

The genus of polynucleotides claimed encompasses an infinite number of polynucleotides of any size (in view of the term "comprising") and function, which share a small structural element, i.e. 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1. As such, the genus claimed not only encompasses species of many different functions but it also encompasses species of different structures since the remainder of a polynucleotide of any size comprising at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1 is completely undefined. The specification is completely silent in regard to the structures of the polynucleotides encompassed by the genus claimed, and discloses a single species, i.e. the polynucleotide of SEQ ID NO: 1. Similarly, the specification provides no clue as to all the functions associated with the genus of polynucleotides claimed, and discloses a single function, i.e. serine protease.

The Examiner disagrees with Appellant's contention that the citations of Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. are completely irrelevant to the question of compliance with 35 USC 112, first paragraph. As previously indicated, the teachings of Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. are extremely relevant to the question of compliance with the written description requirement under 35 USC 112, first paragraph because these references provide clear evidence that polynucleotides or polypeptides sharing common structural elements (i.e. structural homologs) may not be functional homologs. (i.e. have different functions), therefore indicating the unpredictability of the art in regard to how structure correlates with function and how one single polynucleotide can not be representative of the genus claimed. In the instant case, while claim 1 encompasses a genus of polynucleotides of any function having at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1, the only function disclosed (i.e. serine protease) is that of the polypeptide encoded by the polynucleotide of SEQ ID NO: 1. Furthermore, even if the genus of claimed polynucleotides was limited to polynucleotides encoding serine proteases, the specification is completely silent in regard to the critical structural elements required in a polynucleotide to encode a serine protease,

nor does it disclose which 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1 are required in a polynucleotide to encode a serine protease. Therefore, it is unclear as to how a genus of polynucleotides having substantial variation in function and structure can be adequately described with the disclosure of one function and one structure.

In regard to Appellant's position that claims 1, 5 and 8 meet the written description requirements since, according to Appellants, (1) disclosure of the sequence itself complies with part (3), i.e. disclosure of a relevant, identifying characteristic, and (2) there is no requirement for functional characteristics if structural characteristics have been disclosed, it is noted that while relevant structural and/or other physical/chemical properties may be sufficient to adequately describe some genera, in the instant case, the claimed genus of polynucleotides cannot be adequately described by one species in view of the substantial variation within the claimed genus. As clearly indicated in the Written Description guidelines (Federal Register Vol. 66, No. 4. page 1106, third column), the written description requirement may be satisfied by sufficient description of a representative number of species. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In the instant case, not only is there substantial functional variation within the genus since the claimed polynucleotides can have any function, but there is also substantial structural variation within the genus since the structural element common to all the members of the genus, i.e. any 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1 (1041 nucleotides long), does not constitute a significant and relevant structural characteristic as the remainder of the structure of any polynucleotide as claimed is completely undefined. It is noted that 24 nucleotides merely constitute 2.3% of the polynucleotide of SEQ ID NO: 1 (24x100/1041). The Written Description guidelines also indicate that for inventions in an unpredictable art, as is the case here, adequate written description of a genus cannot be achieved by disclosing only one species within the genus. Therefore, one cannot reasonably conclude

that one species is representative of a genus of polynucleotides when there is substantial structural and functional variation within the genus.

In page 20 of the Brief, last paragraph, Appellants submit that the Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991) held that an Applicant must convey with reasonable clarity to those of skill in the art that, as of the filing date sought, he or she was in possession of the claimed invention. Appellants further cite *In re Gosteli* and *Utter v. Hiraga* to support the argument that it is not required to describe exactly what is being claimed and that it is not necessary to describe every single species encompassed by the claims. It is Appellant's opinion that all that is required to comply with 35 USC 112, first paragraph is to convey the invention with reasonably clarity to the skilled artisan.

While the Examiner acknowledges the findings in *Vas-Cath Inc. v. Mahurkar, In re Gosteli,* and *Utter v. Hiraga*, it is noted that the instant rejection was applied in view of the fact that while the claims encompass a genus having substantial structural and functional variation, the specification discloses only a single species of the claimed genus. Therefore, one cannot reasonably conclude that the disclosure of a single species can convey with reasonable clarity that, as of the filing date sought, Appellants were in possession of the invention, i.e. a genus of polynucleotides of any function having at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1 Furthermore, while it is agreed that it is not required to disclose all species in a genus to comply with the written description requirement, it is noted that the single species disclosed is not representative of the entire genus in view of the substantial variation within the claimed genus as previously discussed. As indicated above, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In the instant case, there is substantial functional and structural variation within the genus since the claimed polynucleotides can have any function, and the structural element common to all the members of the genus, i.e. any 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1 (1041 nucleotides

long), is not a significant and relevant structural characteristic as the remainder of the structure of any polynucleotide as claimed is completely undefined.

In page 21 of the Brief, first paragraph, Appellants indicate that the Federal Circuit in *Fiers v. Revel* (25 USPQ2d 1601, 1606, Fed. Cir. 1993) has held that an adequate description of a chemical genus requires a precise definition such as by structure, formula, chemical name or physical properties sufficient to distinguish the genus from other materials. Therefore, according to Appellants, disclosure of a structure, i.e. nucleotide sequence, renders the application in compliance with 35 USC 112, first paragraph. In addition, Appellants cite *Univ. of California v. Eli Lilly and Co.* (43 USPQ2d 1398, 1406, Fed. Cir. 1997) to support the argument that describing a genus of nucleic acids by structure, formula, chemical name or physical properties is sufficient to meet the written description requirements of 35 USC 112, first paragraph, and assert that as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers v. Revel*, the claimed polynucleotides are not distinguished on the basis of function or a method of isolation, but rather by structural features, i.e. the sequence itself. It is Appellant's opinion that using the nucleic acid disclosed in the application, one of skill in the art would be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides lacking at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1 are not members of the genus. Appellant's submit that as indicated in the Final Action and Advisory Action, the genus claimed share a common structural feature, which is all that is required for claims 1, 5 and 8 to meet the written description requirements of 35 USC 112, first paragraph.

While the Examiner agrees that the claimed polynucleotides must share a common structural feature, i.e. at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1, and acknowledges the findings in *Fiers v. Revel* and *Univ. of California v. Eli Lily and Co.*, it is noted that claimed genus is one of substantial variation in function and structure. As indicated above, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative

number of species sufficient to show applicants were in possession of the claimed genus. A representative number of species means that the species that are adequately described are representative of the entire genus. In the instant case, one cannot reasonably conclude that the single species disclosed, i.e. SEQ ID NO: 1, is representative of the claimed genus in view of the fact that the claimed polynucleotides can potentially have many functions which are undisclosed, and the structural element required in all members of the genus, i.e. at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1, is not considered a substantial structural feature since the remainder of the structure of any polynucleotide as claimed is completely undefined. In view of the teachings of Bork, Broun et al., Brenner, Smith et al., Van de Loo et al., Seffernick et al. and Witkowski et al., one of skill in the art would recognize that the claimed invention belongs to an unpredictable art which cannot be adequately described by disclosing a single species. Therefore, one cannot reasonably conclude that the polynucleotide of SEQ ID NO: 1 is sufficient to adequately described all features and attributes of polynucleotides comprising at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1, vectors comprising said polynucleotides, and host cells comprising said vectors.

E. Are claims 1, 5 and 8 enabled?

In page 22 of the Brief, last paragraph, and page 23, first paragraph, Appellants argue that, as set forth in section VIII(D) of the Brief, the citations of Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. are completely irrelevant to the question of compliance with 35 USC 112, first paragraph. Appellants submit that the significant commercial exploitation of nucleic acids requires no more information than the nucleic acid sequence itself. Appellants assert that practicing applications such as gene expression analysis or chromosomal mapping, as described in section VIII(A) of the Brief, requires utilizing nucleic acid sequences and techniques which are well known in the art. It is Appellant's position that the widespread commercial exploitation of nucleic acid sequence information is indicative of

the skill in the art, and that the specification provides sufficient guidance in regard to the various uses of the claimed polynucleotides, all of which is all that is required to meet the enablement requirement under 35 USC 112, first paragraph..

As indicated above, an infinite number of polynucleotides of any size (in view of the term "comprising") and function, which share a small structural element, i.e. 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1, are claimed. As such, the polynucleotides claimed not only can have many different functions but they can be very different in structure since the remainder of a polynucleotide of any size comprising at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1 is completely undefined. It is reiterated herein that the specification provides no additional structural information in regard to the infinite number of polynucleotides encompassed by the claims, with the exception of the polynucleotide of SEQ ID NO: 1. Therefore, Appellant's arguments in regard to the enablement of the claimed polynucleotides since for commercial exploitation of nucleic acids all that is needed is the nucleic acid sequence, are found without merit in view of the fact that the nucleic acid sequences for the polynucleotides claimed have not been disclosed, with the exception of the polynucleotide of SEQ ID NO: 1. In the absence of the nucleic acid sequence for the claimed polynucleotides, it is unclear as to such polynucleotides can be enabled for commercial exploitation as asserted by Appellants. Even if the polynucleotide of SEQ ID NO: 1 is found to have patentable utility, it is noted that the claimed genus of polynucleotides is not enabled in view of the fact that the specification provides no teaching or suggestion as to how to make and/or use the remainder of polynucleotides comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1.

The Examiner disagrees with Appellant's contention that the citations of Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. are completely irrelevant to the question of compliance with 35 USC 112, first paragraph. As previously indicated, the teachings of Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al., as well as those of Bork, Brenner and Smith et al., are

extremely relevant to the question of compliance with the enablement requirement under 35 USC 112, first paragraph because these references, in addition to demonstrating that the scope of the claims encompasses polynucleotides of any function, are also evidence of the unpredictability of the art in regard to accurately determining function based on structural homology. Furthermore, these references provide clear evidence that determining the function of structural homologs using structural homology (i.e. sequence similarity) alone is not sufficient and that one may require experimental evidence to confirm function. Therefore, since the scope of the claims encompass an infinite number of polynucleotides of any function and the specification discloses a single function, i.e. serine protease, determining the functions, i.e. how to use, of all the polynucleotides encompassed by the claims would result in undue experimentation in the absence of any teaching or suggestion as to the functions of other polynucleotides as encompassed by the claims. Moreover, even determining which of the extremely large number of polynucleotides encompassed by the claims encode serine proteases would be undue experimentation if one considers the teachings of the art in regard to the unpredictability of assigning function based on structural homology and the fact that the specification is completely silent in regard to the critical structural elements required in a polynucleotide comprising at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1 to encode a serine protease, or which 24 nucleotides of the polynucleotide of SEQ ID NO: 1 are essential to encode a serine protease. As such, one of skill in the art is left with an enormous number of polynucleotides to test without any clue or guidance as to which ones are more likely to encode a serine protease.

While the Examiner agrees that applications such as gene expression analysis or chromosomal mapping can be practiced with techniques well known in the art, the Examiner disagrees with Appellant's contention that the widespread commercial exploitation of nucleic acid sequence information is evidence of the level of skill in the art as it relates to the enablement of the instant invention and that all that is required to meet the enablement requirement set forth in 35 USC 112, first paragraph is the disclosure of

the nucleic acid sequence. The Examiner is not disputing that nucleic acid sequence information is used in many different commercial and non-commercial endeavors. However, in the instant case, commercial exploitation of the instant nucleic acid sequences is not considered a patentable use since such use is not specific as the disclosure of any nucleic acid sequence can add to the current nucleic acid sequence information. In regard to uses such as gene expression analysis or chromosomal mapping, while it is agreed that such uses would be enabled for the polynucleotide of SEQ ID NO: 1 if it is found to have specific and substantial utility, it is unclear as to how one of skill in the art can reasonably conclude that polynucleotides comprising at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1 are enabled to be used in gene expression analysis or chromosomal mapping if the biological functions are completely unknown and the specification is silent in regard to the chromosomal location of all polynucleotides encompassed by the claims, with the exception of the polynucleotide of SEQ ID NO: 1. In the absence of any information as to the biological functions of polynucleotides comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1, it is unclear as to how one can use the claimed polynucleotides in gene expression analysis since determining the expression levels of a polynucleotide is meaningless if it cannot be correlated to a specific biological process, condition and/or disease. It is also noted that while any fragment of the polynucleotide of SEQ ID NO: 1 can be used as a probe to detect the polynucleotide of SEQ ID NO: 1, not every polynucleotide comprising at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1 can be used as a probe to detect the polynucleotide of SEQ ID NO: 1. Due to the fact that the claimed polynucleotides can be of any length, they may have very little overall structural similarity to the polynucleotide of SEQ ID NO: 1 such that they would not hybridize to the polynucleotide of SEQ ID NO: 1 and could not be used as probes. Therefore, even those uses cited by Appellants do not meet the "how to use" requirement of 35 USC 112, first paragraph for the full scope of claimed nucleic acids. As such, one cannot reasonably conclude that the claims meet the enablement

requirement under 35 USC 112, first paragraph by merely reciting a structural limitation, i.e. 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1.

In page 23 of the Brief, last paragraph, Appellants cite *In re Angstadt and Griffin, In re Wands, and Amgen Inc. v Chugai Pharmaceutical Co., Ltd.* as evidence to support the argument that the need for some experimentation is not a basis for lack of enablement and that while some experimentation may be required to practice the claimed invention, such experimentation may be permissible if routinely practiced in the art.

The Examiner acknowledges the findings in *In re Angstadt and Griffin, In re Wands, and Amgen Inc. v Chugai Pharmaceutical Co., Ltd.* However, it is noted that the instant claims were not rejected due to the need for some routine experimentation as asserted but rather due to the undue experimentation required to practice the full scope of the claimed invention. As indicated above, practicing the full scope of the claimed invention requires determination of function for the claimed polynucleotides. While one function has been disclosed by the specification in regard to the polynucleotide of SEQ ID NO: 1, the remaining functions for the polynucleotides as claimed is unknown. As repeatedly stated by the Examiner, the art, as evidenced by the teachings of Bork, Broun et al., Brenner, Smith et al., Van de Loo et al., Seffernick et al. and Witkowski et al., teaches the unpredictability of determining function based on structural homology (i.e. sequence homology). In addition, even if the claimed invention is limited to polynucleotides encoding a serine protease and having the recited structural limitation, the specification provides no clue as to which are the structural elements required in a polynucleotide comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1 to encode a serine protease, nor does it disclose which are the 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1 required to encode a protein having serine protease function. The Examiner is not contesting that testing a limited number of structural homologs of the polynucleotide of SEQ ID NO: 1 to determine if they encode serine proteases does not constitute undue experimentation if some knowledge or guidance has been provided in

regard to how structure correlates with function. However, in the instant case, practicing the full scope of the invention requires testing of an infinite number of polynucleotides for which the specification provides (1) no information in regard to their function, and (2) no structure/function correlation, in order to determine their function.

In page 24 of the Brief, first paragraph, Appellants argue that there is sufficient knowledge and skill in the art for a skilled artisan to know how to make and use the claimed polynucleotides entirely without the need for further details in a patent application. Appellants submit that a Ph.D. level molecular biologist can use the disclosed nucleotide sequence to design probes and primers and use them in screening and detection methods. Appellants further submit that the specification discloses techniques which can be used in many different aspects of the claimed invention such as those taught by Sambrook et al. (Molecular Cloning, A Laboratory Manual) and Ausbel et al. (Current Protocols in Molecular Biology). Appellants cite *Ex parte Schwarze, In re Marzocchi, In re Wands,* and *Hybritech Inc. v Monoclonal Antibodies Inc.* to support the argument that a patent need not disclose what is well known in the art and that lack of express teaching is insufficient to support an enablement rejection if one of skill in the art would know how to perform at least one aspect of the invention. It is Appellant's opinion that standard molecular biology techniques are routine in the art and they do not need to be described in detail.

The Examiner agrees that (1) a Ph.D. level molecular biologist would know how to design probes and primers, (2) a patent need not disclose what is well known in the art, and (3) standard molecular biology techniques are well known and are not required to be described in detail in the specification. The Examiner however, disagrees with Appellant's contention that what is known in the art and the disclosure of a single polynucleotide is sufficient for an skilled artisan to know how to make and use the claimed invention. While the argument can be made that making the claimed polynucleotides does not constitute undue experimentation due to the fact that many molecular biology techniques are known in the art which would allow one of skill in the art to make the claimed polynucleotides, determining how to use the

claimed polynucleotides, particularly in view of the fact that their functions have not been disclosed, constitute undue experimentation. As indicated above, while a patent application does not have to teach what is well known in the art, it is noted that neither the specification nor the art teaches the function of the claimed polynucleotides. In the absence of any teaching or suggestion as to the functions of the claimed polynucleotides, either by the specification or the art, the complete lack of information as to how structure correlates with the only function disclosed in the specification, and in view of the unpredictability of the art in regard to determining function based on structural homology, one of skill in the art would have to go through the burden of undue experimentation in order to practice the full scope of the claimed invention.

In page 25 of the Brief, Appellants cite *In re Brana* and state that the Federal Circuit admonished the PTO for confusing the requirements under the law for obtaining a patent and those required for government approval to market a drug for human consumption. Appellants further cite *In re Naquin* and *In re Moore* to support the argument that the specification need describe the invention only in such detail as to enable one of skill in the art to make and use it and that the enablement analysis should consider the level of skill possessed by one of ordinary skill in the pertinent art.

The Examiner acknowledges *In re Brana, In re Naquin* and *In re Moore*, however it is noted that (1) the instant claims have not been rejected because they fail to comply with government requirements to market a drug for human consumption, and (2) the enablement analysis has taken into consideration what is considered well known in the art. As repeatedly stated by the Examiner, the instant claims have been rejected in view of the fact that in order to practice the full scope of the claims, one of skill in the art would require to know the function of the claimed polynucleotides. The specification, while providing the structure of the polynucleotide of SEQ ID NO: 1 and asserting one function for such polynucleotide, provides no clue as to the functions of other polynucleotides, the critical structural elements required in a polynucleotide having at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1 to encode a serine

protease, or even which 24 nucleotides of the polynucleotide of SEQ ID NO: 1 are required in a polynucleotide to encode a serine protease. Therefore, in the instant case, the specification is not enabling for the full scope of the claims since it fails to disclose information which is not found in the teachings of the art and is essential for one of skill in the art to practice the claimed invention.

In page 25 of the Brief, last paragraph, Appellants cite *In re Nelson, Cross v. Iizuka*, and *Johns Hopkins University v. Cell Pro Inc.* as evidence to support the argument that claims are enabled by defining any practical use. Appellants submit that the specification discloses numerous applications for the claimed polynucleotides, such as to track gene expression in gene chips. It is Appellant's contention that since many public domain nucleotide sequences which have not been associated with a specific biological function are used everyday in gene chip applications, it is not logical that undue experimentation is required to use the claimed polynucleotides, which according to Appellants, have been biologically validated as polynucleotides having a coding sequence (i.e. encode proteins), in the very same gene chip applications.

The Examiner acknowledges the findings in *In re Nelson*, *Cross v. Iizuka*, and *Johns Hopkins University v. Cell Pro Inc.*, however it is noted that even if the polynucleotide of SEQ ID NO: 1 is found to have utility, the specification does not provide enablement for all the polynucleotides claimed, i.e. polynucleotides having at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1, in view of the complete lack of information as to other functions which may be associated with the claimed polynucleotides and the lack of information as to any structure/function correlation between the polynucleotide of SEQ ID NO: 1, or fragments thereof, and serine proteases or any other function. In regard to the argument that the claimed polynucleotides should be enabled for use in gene chip applications since other public domain polynucleotides can be used in gene chip applications, it is noted that the Examiner is not arguing that the claimed polynucleotide cannot be physically placed in a gene chip but rather how one of skill in the art would have a practical use for the claimed polynucleotides in

gene chip applications in the absence of any information as to the functions of the claimed polynucleotides. While it is agreed that many polynucleotides known in the public domain may be used in gene chip applications, it is reiterated that in gene chip applications, such as gene expression analysis, determining the expression levels of a polynucleotide is meaningless if it cannot be correlated to a specific biological process, condition and/or disease. It is also reiterated that while any fragment of the polynucleotide of SEQ ID NO: 1 can be used in gene chip applications as a probe to detect the polynucleotide of SEQ ID NO: 1, not every polynucleotide comprising at least 24 nucleotides of the polynucleotide of SEQ ID NO: 1 can be used as a probe to detect the polynucleotide of SEQ ID NO: 1, in view of the fact that since the claimed polynucleotides can be of any length, they may have very little overall structural similarity to the polynucleotide of SEQ ID NO: 1 such that they would not hybridize to the polynucleotide of SEQ ID NO: 1.

While the Examiner disagrees with Appellant's contention that the polynucleotide of SEQ ID NO: 1 has been biologically validated as a coding polynucleotide for the reasons already discussed in regard to the utility rejection, even if one assumes that the polynucleotide of SEQ ID NO: 1 is a coding polynucleotide which encodes a serine protease associated with a specific biological process and/or for which a substrate has been disclosed, it is noted that the specification has not disclosed any biological validation of other polynucleotides having at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1, such that it would be apparent that any polynucleotide as claimed is a coding polynucleotide. Furthermore, the specification has provided no clue as to the polypeptides which would be encoded by such polynucleotides or their functions. Therefore, while one could argue that the polynucleotide of SEQ ID NO: 1 can be used in gene chip applications if its biological function is known, it is unclear as to how one of skill in the art can reasonably conclude that polynucleotides of any function comprising at least 24 contiguous nucleotides of the polynucleotide of SEQ ID NO: 1 can have a

practical use in gene chip applications as asserted by Appellants by merely disclosing the structure of the polynucleotide of SEQ ID NO: 1.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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DR
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